Olaparib tablets as maintenance therapy in patients with platinum-sensitive, relapsed ovarian cancer and a *BRCA1/2* mutation (SOLO2/ENGOT-Ov21): a double-blind, randomised, placebo-controlled, phase 3 trial

*Eric Pujade-Lauraine, Jonathan A Ledermann, Frédéric Selle, Val Gebski, Richard T Penson, Amit M Oza, Jacob Korach, Tomasz Huzarski, Andrés Poveda, Sandro Pignata, Michael Friedlander, Nicoletta Colombo, Philipp Harter, Keiichi Fujiwara, Isabelle Ray-Coquard, Susana Banerjee, Joyce Liu, Elizabeth S Lowe, Ralph Bloomfield, Patricia Pautier, the SOLO2/ENGOT-Ov21 investigators**

Summary

Background Olaparib, a poly(ADP-ribose) polymerase (PARP) inhibitor, has previously shown efficacy in a phase 2 study when given in capsule formulation to all-comer patients with platinum-sensitive, relapsed high-grade serous ovarian cancer. We aimed to confirm these findings in patients with a *BRCA1* or *BRCA2* (*BRCA1/2*) mutation using a tablet formulation of olaparib.

Methods This international, multicentre, double-blind, randomised, placebo-controlled, phase 3 trial evaluated olaparib tablet maintenance treatment in platinum-sensitive, relapsed ovarian cancer patients with a *BRCA1/2* mutation who had received at least two lines of previous chemotherapy. Eligible patients were aged 18 years or older with an Eastern Cooperative Oncology Group performance status at baseline of 0–1 and histologically confirmed, relapsed, high-grade serous ovarian cancer or high-grade endometrioid cancer, including primary peritoneal or fallopian tube cancer. Patients were randomly assigned 2:1 to olaparib (300 mg in two 150 mg tablets, twice daily) or matching placebo tablets using an interactive voice and web response system. Randomisation was stratified by response to previous platinum chemotherapy (complete *vs* partial) and length of platinum-free interval (6–12 months *vs* ≥12 months) and treatment assignment was masked for patients, those giving the interventions, data collectors, and data analysers. The primary endpoint was investigator-assessed progression-free survival and we report the primary analysis from this ongoing study. The efficacy analyses were done on the intention-to-treat population; safety analyses included patients who received at least one dose of study treatment. This trial is registered with ClinicalTrials.gov, number NCT01874353, and is ongoing and no longer recruiting patients.

Findings Between Sept 3, 2013, and Nov 21, 2014, we enrolled 295 eligible patients who were randomly assigned to receive olaparib (n=196) or placebo (n=99). One patient in the olaparib group was randomised in error and did not receive study treatment. Investigator-assessed median progression-free survival was significantly longer with olaparib (19·1 months [95% CI 16·3–25·7]) than with placebo (5·5 months [5·2–5·8]; hazard ratio [HR] 0·30 [95% CI 0·22–0·41], p<0·0001). The most common adverse events of grade 3 or worse severity were anaemia (38 [19%] of 195 patients in the olaparib group *vs* two [2%] of 99 patients in the placebo group), fatigue or asthenia (eight [4%] *vs* two [2%]), and neutropenia (ten [5%] *vs* four [4%]). Serious adverse events were experienced by 35 (18%) patients in the olaparib group and eight (8%) patients in the placebo group. The most common in the olaparib group were anaemia (seven [4%] patients), abdominal pain (three [2%] patients), and intestinal obstruction (three [2%] patients). The most common in the placebo group were constipation (two [2%] patients) and intestinal obstruction (two [2%] patients). One (1%) patient in the olaparib group had a treatment-related adverse event (acute myeloid leukaemia) with an outcome of death.

Interpretation Olaparib tablet maintenance treatment provided a significant progression-free survival improvement with no detrimental effect on quality of life in patients with platinum-sensitive, relapsed ovarian cancer and a *BRCA1/2* mutation. Apart from anaemia, toxicities with olaparib were low grade and manageable.

Funding AstraZeneca.

Lancet Oncol 2017

Published **Online** July 25, 2017 http://dx.doi.org/10.1016/S1470-2045(17)30469-2

See **Online/Comment** http://dx.doi.org/10.1016/S1470-2045(17)30567-3

*Members listed in the appendix

Medical Oncology Department, Université Paris Descartes, AP-HP, Paris, France (Prof E Pujade-Lauraine MD); **Department of Oncology, University College London, London, UK** (Prof J A Ledermann MD); **Hôpital Tenon, Paris, France** (F Selle MD); **Department of Biostatistics and Research Methodology, University of Sydney, Sydney, NSW, Australia** (Prof V Gebski FRANZCR); **Department of Hematology/Oncology, Massachusetts General Hospital, Boston, MA, USA** (R T Penson MD); **Princess Margaret Cancer Centre, Toronto, Canada** (Prof A M Oza MD); **Gynecologic Oncology Department, Sheba Medical Center, Tel Aviv University, Tel Hashomer, Israel** (J Korach MD); **Department of Genetics and Pathology, Pomeranian Medical University, Szczecin, Poland** (T Huzarski PhD); **Instituto Valenciano de Oncología, Valencia, Spain** (A Poveda MD); **Istituto Tumori Pascale di Napoli, Naples, Italy** (Prof S Pignata MD); **Department of Medical Oncology, University of New South Wales Clinical School, Prince of Wales Hospital, Randwick, NSW, Australia** (Prof M Friedlander MBChB); **Gynecology Department, University of Milan-Bicocca and Istituto Europeo Oncología, Milan, Italy**

Introduction

Patients with advanced ovarian cancer often respond well to first-line chemotherapy, with the subsequent chemotherapy-free interval before disease progression usually ranging from 4 to 12 months.[1–3] After disease recurrence, however, this chemotherapy-free interval becomes progressively shorter with the successive treatments given at each subsequent relapse. A substantial unmet need exists for well tolerated therapies that can improve long-term disease control in patients with recurrent ovarian cancer.

Olaparib is the first-in-class oral poly(ADP-ribose) polymerase (PARP) inhibitor. The inhibition of PARP is a potential synthetic lethal therapeutic strategy for

(Prof N Colombo MD); **Department of Gynecology and Gynecologic Oncology, Kliniken Essen Mitte, Essen, Germany** (P Harter MD); **Department of Gynecologic Oncology, Saitama Medical University International Medical Center, Saitama, Japan** (Prof K Fujiwara MD); **Medical Oncology Department, Centre Léon Bérard and University Claude Bernard, Lyon, France** (Prof I Ray-Coquard MD); **The Royal Marsden NHS Foundation Trust, London, UK** (S Banerjee PhD); **Dana-Farber Cancer Institute, Boston, MA, USA** (J Liu MD); **AstraZeneca, Gaithersburg, MD, USA** (E S Lowe MD); **AstraZeneca, Cambridge, UK** (R Bloomfield MSc); **Gustave Roussy Cancer Campus, Villejuif, France** (P Pautier MD)

Correspondence to:
Prof Eric Pujade-Lauraine, Hôpital Hôtel-Dieu, Place Jean-Paul II, 75004, Paris, France
epujade@arcagy.org

Research in context

Evidence before this study

We searched PubMed and the databases of the American Society of Clinical Oncology, European Cancer Organisation, European Society of Gynaecological Oncology, European Society for Medical Oncology, and Society of Gynaecological Oncology for articles and conference abstracts published between Jan 1, 2016, and Jan 1, 2017, including the search terms "poly(ADP-ribose) polymerase inhibitor" or "PARP inhibitor" and "ovarian cancer", using no language restrictions. Poly(ADP-ribose) polymerase (PARP) inhibitors in late clinical development are olaparib, niraparib, rucaparib, talazoparib, and veliparib. In a previous phase 2 trial (Study 19), patients with platinum-sensitive, relapsed ovarian cancer treated with the oral PARP inhibitor olaparib as maintenance monotherapy (capsule formulation) had significantly longer progression-free survival than those treated with placebo, with the greatest progression-free survival benefit recorded in patients with a *BRCA1/2* mutation.

Added value of this study

To our knowledge, we report here the first phase 3 data for the new tablet formulation of olaparib as monotherapy, rather than the capsule formulation, in patients with ovarian cancer. Efficacy data from this SOLO2 trial show a significant improvement in median progression-free survival with maintenance olaparib compared with placebo, by investigator assessment and blinded independent central review, which substantially exceeded the progression-free survival benefit recorded with olaparib in Study 19. We also recorded a significant improvement in time to second progression, and a significant and clinically meaningful improvement in times to first or second subsequent therapy or death with olaparib versus placebo. The new tablet formulation of olaparib reduced the pill burden from 16 capsules to four tablets per day while maintaining similar or higher exposure, providing patients with a simpler, more convenient treatment regimen. Maintenance treatment with the olaparib tablet formulation was well tolerated, with no new safety signals and manageable toxicities. Additionally, we found no significant difference in patients' quality of life with olaparib compared with placebo.

Implications of all of the available evidence

The sensitivity analysis of progression-free survival by blinded independent central review showed the greatest median improvement in progression-free survival observed so far for a PARP inhibitor in this clinical setting, and resulted in a lower hazard ratio in favour of olaparib than that of the investigator-assessed primary endpoint. Both assessments of progression-free survival showed a progression-free survival benefit with olaparib that substantially exceeded that seen in a phase 2 investigation in patients with platinum-sensitive, relapsed ovarian cancer and a *BRCA1/2* mutation. The SOLO2 data support use of the olaparib tablet formulation, which was shown to have a similar safety profile to that previously seen with the approved capsule formulation of olaparib. The reduced pill burden might contribute to improved patient compliance. Given the few treatment options available for patients with platinum-sensitive, relapsed ovarian cancer, the data for olaparib as maintenance therapy in SOLO2 are notable: patients showed a delay in disease progression while experiencing no change in their quality of life. Additional clinical studies using the olaparib tablet formulation are ongoing.

treatment of cancers characterised by specific DNA repair defects, such as tumour cells that harbour a *BRCA1* or *BRCA2* (*BRCA1/2*) mutation and are rendered deficient in homologous recombination repair.[4,5] In homologous recombination-deficient tumours, PARP inhibition eliminates an alternative DNA repair pathway essential for maintaining viability, leading to tumour cell death. The estimated prevalence of a *BRCA1/2* mutation in patients with newly diagnosed high-grade serous ovarian cancer is 20–25%, and might be higher in patients with platinum-sensitive, relapsed ovarian cancer.[6–9] Olaparib (capsule formulation) is currently approved in the European Union and other countries as maintenance treatment for patients with platinum-sensitive, relapsed ovarian cancer and a germline or somatic *BRCA1/2* mutation, and in the USA as monotherapy for advanced ovarian cancer patients with a germline *BRCA1/2* mutation.[10,11]

Previous studies have indicated the effectiveness of olaparib in the setting of platinum-sensitive, relapsed, high-grade serous ovarian cancer. Study 19 (NCT00753545) was a randomised, controlled, phase 2 trial of olaparib capsules given as maintenance monotherapy to 265 patients, which showed a significant improvement in progression-free survival compared with placebo in the total study population (hazard ratio [HR] 0·35, 95% CI 0·25–0·49; p<0·001).[12] A preplanned retrospective analysis of patients in Study 19 by *BRCA* status suggested that those with a *BRCA1/2* mutation derived the greatest progression-free survival benefit from olaparib treatment (HR 0·18, 95% CI 0·10–0·31; p<0·0001).[2,12] Study 19 also showed the long-term benefit and tolerability profile of olaparib in the maintenance setting.[13]

Our trial was designed to prospectively confirm the findings seen in Study 19 in a similar disease setting: it is an international, multicentre, randomised, phase 3 trial to evaluate olaparib maintenance treatment in patients with platinum-sensitive, relapsed ovarian cancer and a *BRCA1/2* mutation. We used a tablet formulation of olaparib that offers patients a reduced daily pill burden compared with capsules. An adaptive-design phase 1 trial of olaparib bioavailability (Study 24; NCT00777582)[14] has previously established that olaparib exposure with a 300 mg twice-daily tablet dose was similar to, or higher than, exposure in patients receiving olaparib 400 mg twice-daily capsule. These findings[14]

informed the tablet dose regimen adopted in our trial and other phase 3 olaparib studies. Here, we report efficacy and safety data from the primary analysis of our ongoing trial.

Methods

Study design and participants

This international, multicentre, double-blind, randomised, placebo-controlled, phase 3 study (SOLO2/ENGOT-Ov21) was done by the European Network for Gynaecological Oncological Trial groups (ENGOT) across 123 sites in 16 countries (appendix pp 2–5). Eligible patients were aged 18 years or older with an Eastern Cooperative Oncology Group (ECOG) performance status at baseline of 0–1 and histologically confirmed, relapsed, high-grade serous ovarian cancer or high-grade endometrioid cancer, including primary peritoneal or fallopian tube cancer. Eligible patients had received at least two previous lines of platinum-based chemotherapy and were in objective response (either complete response or partial response according to modified Response Evaluation Criteria in Solid Tumors [RECIST] version 1.1 or CA-125 levels) to their most recent regimen. Patients were also required to have platinum-sensitive disease (disease progression occurring at least 6 months after the last dose of platinum therapy was given) following their penultimate line of chemotherapy before enrolment.

Patients were required to have a predicted deleterious, or suspected deleterious, *BRCA1/2* mutation based on either blood or tumour testing, and all patients had to consent to provide two blood samples for confirmatory germline *BRCA1/2* mutation testing using the Myriad Genetics *BRCA* test (Myriad BRACAnalysis; Myriad Genetics, Salt Lake City, UT, USA). Patients with a known *BRCA1/2* mutation before randomisation could enter the trial on the basis of this information; patients with unknown *BRCA1/2* mutation status were screened before randomisation. Patients were required to have normal organ and bone marrow function measured within 28 days of randomisation. Patients were ineligible if they had received previous treatment with a PARP inhibitor, had received any systemic chemotherapy or radiotherapy (unless palliative) within 3 weeks prior to study treatment, or had drainage of their ascites during the final two cycles of their last chemotherapy regimen before enrolment. Patients with symptomatic uncontrolled brain metastases or another malignancy within the past 5 years were also ineligible (see appendix p 7 for exceptions), as were patients with myelodysplastic syndrome or acute myeloid leukaemia, immunocompromised patients, and those with active hepatitis B or C infection. Full eligibility criteria are provided in the appendix (pp 6–8). All patients provided written, informed consent. This study was done in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.[15] The latest protocol is available in the appendix.

Randomisation and masking

Eligible patients were randomised (2:1) to receive olaparib tablet maintenance monotherapy or matching placebo. The randomisation scheme was produced by a computer software program that generates random numbers (Global Randomisation System) and was loaded into an interactive voice and web response system database. Investigators (or nominated assistants) contacted the interactive voice and web response system centralised randomisation centre for allocation of randomised therapy. Randomisation was completed within 8 weeks of the patients' last dose of chemotherapy, and was stratified by response to previous chemotherapy (complete *vs* partial) and length of platinum-free interval (6–12 months *vs* ≥12 months). Treatment masking was achieved using individual treatment codes assigned by the interactive voice and web response system. Treatment assignment was masked for patients, those giving the interventions, data collectors, and data analysers. Olaparib and placebo tablets were manufactured by AstraZeneca (Macclesfield, UK), looked identical, and were presented in the same packaging. Unmasking was only permitted in medical emergencies where appropriate management of the patient required knowledge of the treatment randomisation.

See Online for appendix

Procedures

Patients received either oral olaparib maintenance monotherapy (300 mg in two 150 mg tablets, twice daily) or matching placebo (tablets twice daily) until disease progression or until the investigator deemed that a patient was no longer benefiting from treatment. If required, toxicities could be managed by treatment interruptions and dose reductions. Repeat dose interruptions were allowed, as needed, for a maximum of 14 days on each occasion of National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE; version 4.0) grade 3–4 toxicity that was considered to be treatment-related by the investigator, until complete recovery or the toxicity reverted to grade 1 or less. If toxicities reoccurred following re-challenge with study treatment, and if further dose interruptions were considered inadequate for the management of toxicity, then a patient could be considered for dose reduction (to 250 mg twice daily and then, if needed, to 200 mg twice daily) or for permanent discontinuation of study treatment. After discontinuation of study treatment, the investigator was responsible for selecting a patient's subsequent treatment.

Patients were assessed using CT or MRI scans every 12 weeks until week 72, and then every 24 weeks thereafter until objective disease progression; we also sent these scans to a clinical research organisation for blinded independent central review. After disease progression, patients were followed every 12 weeks for second progression and survival. Patient-reported health-related quality of life was assessed with the Trial Outcome Index (TOI) score, derived from the Functional Assessment of

Cancer Therapy–Ovarian Cancer (FACT-O) questionnaire; patient-reported health state utility was assessed with the EuroQoL five-dimensions five-level questionnaire. Questionnaires were collected every 12 weeks for either 24 months or until the data cutoff for the primary analysis (whichever occurred first). Safety was monitored by recording adverse events, measuring haematology, clinical chemistry, and vital signs, and doing physical examinations. Adverse events were graded according to NCI CTCAE version 4.0. Safety assessments comprised measurements of haematology and clinical chemistry (on days 1, 8, 15, 22, 29, then every 4 weeks from the next visit [visit 7] until week 72, then every 12 weeks thereafter) and measurements of vital signs and physical examinations (on day 1, then every 4 weeks until week 72, then every 12 weeks thereafter).

Outcomes

The primary endpoint was investigator assessment of progression-free survival, defined as the time from randomisation until objective radiological disease progression or death using modified RECIST version 1.1. A sensitivity analysis of progression-free survival was done by blinded independent central review. Secondary endpoints were time to first subsequent therapy or death; time to second subsequent therapy or death; time to study treatment discontinuation or death; time to second progression (determined by RECIST, serum CA-125 levels, or symptomatic progression); time to earliest progression (by RECIST or CA-125 levels) or death; investigator assessment of overall survival; safety and tolerability; and health-related quality of life (change from baseline in TOI score of FACT-O). Secondary endpoints also included efficacy of olaparib according to *BRCA1/2* gene variants and exposure to olaparib in patients in the olaparib group, which will be reported elsewhere. We used preplanned subgroup analyses for progression-free survival to evaluate the consistency of the treatment effect across several prognostic factors including previous administration of bevacizumab and presence of a Myriad Genetics-confirmed *BRCA1/2* mutation as part of the trial.

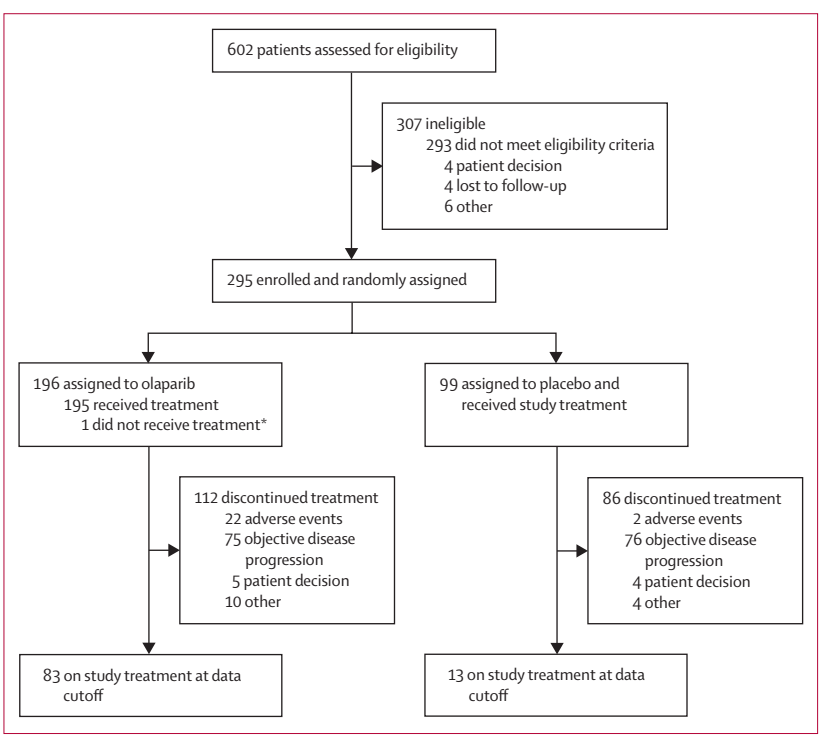

Figure 1: **Trial profile**
*Randomised in error (owing to ineligibility for the trial) and therefore did not receive study treatment.

Statistical analysis

We aimed to analyse a higher number of events than required for a powered superiority analysis for both progression-free survival and time to second progression; therefore, the power to show superiority for both endpoints was greater than 90%. In total, 192 events of progression or death (~65% maturity) were required to provide sufficient precision of the estimated HR. We tested progression-free survival at a two-sided significance level of 5% and analysed it with a log-rank test, using the randomisation stratification factors. The sensitivity analysis of progression-free survival by blinded independent central review used the same methods and model as for the primary analysis of progression-free survival. We analysed time to second progression and overall survival at the time of primary analysis of progression-free survival, using the same methods. At this initial analysis, we would declare statistical significance for time to second progression if one-sided $p<0·0125$ and for overall survival if one-sided $p<0·0001$. We used SAS version 9.1.3 for all analyses.

We analysed efficacy data and patient-reported outcomes in the intention-to-treat population, which included all randomised patients (full analysis set). We analysed safety in all patients from the intention-to-treat population who received at least one dose of study treatment (safety analysis set). Patients were required to have both an evaluable score at baseline and at least one evaluable follow-up form to be assessable for health-related quality of life. We defined an evaluable form as one having at least one subscale that could be measured, or a form that was not completed because the patient was deemed too heavily affected by symptoms of disease. Patients who did not fulfil these requirements were deemed as not assessable for health-related quality of life.

The statistical analysis plan is available in the appendix. This trial is registered with ClinicalTrials.gov number NCT01874353 and is closed to new participants. Patients are in follow-up for overall survival and the trial remains ongoing.

Role of the funding source

The trial design was a collaboration between Groupe des Investigateurs Nationaux pour l'Etude des Cancers

Ovariens et du sein (GINECO), ENGOT, and the sponsor, AstraZeneca. This Article was written by the authors, with medical writing support funded by the sponsor. All authors had full access to the raw data and had roles in data collection, analysis, and interpretation, and manuscript writing. The decision to submit the manuscript for publication was made by all the authors. The corresponding author had full access to all the raw data and had final responsibility for the decision to submit for publication.

Results

Between Sept 3, 2013, and Nov 21, 2014, 602 patients were assessed for eligibility, of whom 295 were enrolled (figure 1). At data cutoff (Sept 19, 2016), 294 (>99%) of 295 randomised patients had received study treatment (one patient was randomised incorrectly to the olaparib group and did not receive study treatment), and 83 (43%) of 195 patients were receiving ongoing treatment with olaparib compared with 13 (13%) of 99 patients remaining on placebo. Demographic and baseline characteristics seemed to be well balanced between the two groups (table 1). 33 (17%) of 196 patients in the olaparib group and 20 (20%) of 99 patients in the placebo group had received treatment with bevacizumab before their final platinum regimen prior to randomisation in this study. 153 (78%) patients in the olaparib group and 83 (84%) patients in the placebo group had a *BRCA1/2* mutation previously determined by local testing and could be enrolled on the basis of this information. All patients received a confirmatory *BRCA* test as part of the trial, which confirmed a germline *BRCA1/2* mutation in 190 (97%) patients in the olaparib group and 96 (97%) in the placebo group (table 1). The Myriad Genetics *BRCA* test did not determine a *BRCA1/2* mutation either to be deleterious or suspected deleterious in nine cases (six in the olaparib group and three in the placebo group): four of these nine patients had variants of unknown significance, two patients were *BRCA1/2* wildtype according to the Myriad Genetics *BRCA* test, and three had a missing confirmatory Myriad Genetics *BRCA* test (because the *BRCA1/2* mutation status of all nine patients had previously been determined by local testing before randomisation, they were still eligible for inclusion). No patients had a confirmed somatic *BRCA1/2* mutation. Details of treatment duration and dose intensity are provided in the appendix (p 9).

We did the efficacy analysis after 187 investigator-assessed events of disease progression or death (63% maturity: 107 [55%] of 196 in the olaparib group *vs* 80 [81%] of 99 in the placebo group). The actual number of progression-free survival events was five (2·6%) fewer than the number detailed in the statistical plan (~192 events). The median follow-up for progression-free survival was 22·1 months (IQR 21·9–27·4) in the olaparib group and 22·2 months (8·3–27·5) for placebo.

Investigator-assessed median progression-free survival was significantly longer in the olaparib group than in the placebo group (19·1 months [95% CI 16·3–25·7] with olaparib *vs* 5·5 months [5·2–5·8] with placebo; HR 0·30 [95% CI 0·22–0·41], p<0·0001; figure 2A). According to the Kaplan-Meier survival estimator, 12-month progression-free survival was 65% (95% CI 57·8–71·4) in the olaparib group versus 21% (13·3–29·6) in the placebo group; 24-month progression-free survival was 43% (35·5–50·4) versus 15% (8·6–23·2). The sensitivity analysis of progression-free survival by blinded independent central review (151 events in

	Olaparib (n=196)	Placebo (n=99)
Age (years)	56 (51–63)	56 (49–63)
ECOG performance status*		
0	162 (83%)	77 (78%)
1	32 (16%)	22 (22%)
Missing	2 (1%)	0
Primary tumour location		
Ovary	164 (84%)	86 (87%)
Fallopian tubes or primary peritoneal	31 (16%)	13 (13%)
Missing	1 (1%)	0
Histology type		
Serous	183 (93%)	86 (87%)
Endometrioid	9 (5%)	8 (8%)
Mixed	3 (2%)	5 (5%)
Missing	1 (1%)	0
Patients with >2 cm target lesions at baseline	30 (15%)	18 (18%)
Confirmed germline *BRCA* mutation		
BRCA1	132 (67%)	61 (62%)
BRCA2	58 (30%)	35 (35%)
Both	0	0
Missing†	6 (3%)	3 (3%)
Response to previous platinum therapy		
Complete	91 (46%)	47 (47%)
Partial	105 (54%)	52 (53%)
Number of previous platinum-based regimens‡		
Two	110 (56%)	62 (63%)
Three	60 (31%)	20 (20%)
Four	18 (9%)	12 (12%)
Five or more	7 (4%)	5 (5%)
Platinum-free interval		
>6–12 months	79 (40%)	40 (40%)
>12 months	117 (60%)	59 (60%)

Data are n (%) or median (IQR). ECOG=Eastern Cooperative Oncology Group. *An ECOG performance status of 0 indicates that the patient is fully active and a status of 1 indicates that the patient is restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature. †Denotes patients with a germline *BRCA1/2* mutation by local testing, but without confirmed germline *BRCA1/2* mutation status by Myriad Genetics *BRCA* testing as part of this trial. ‡One patient in the olaparib group had an unknown number of previous regimens.

Table 1: **Baseline and demographic characteristics**

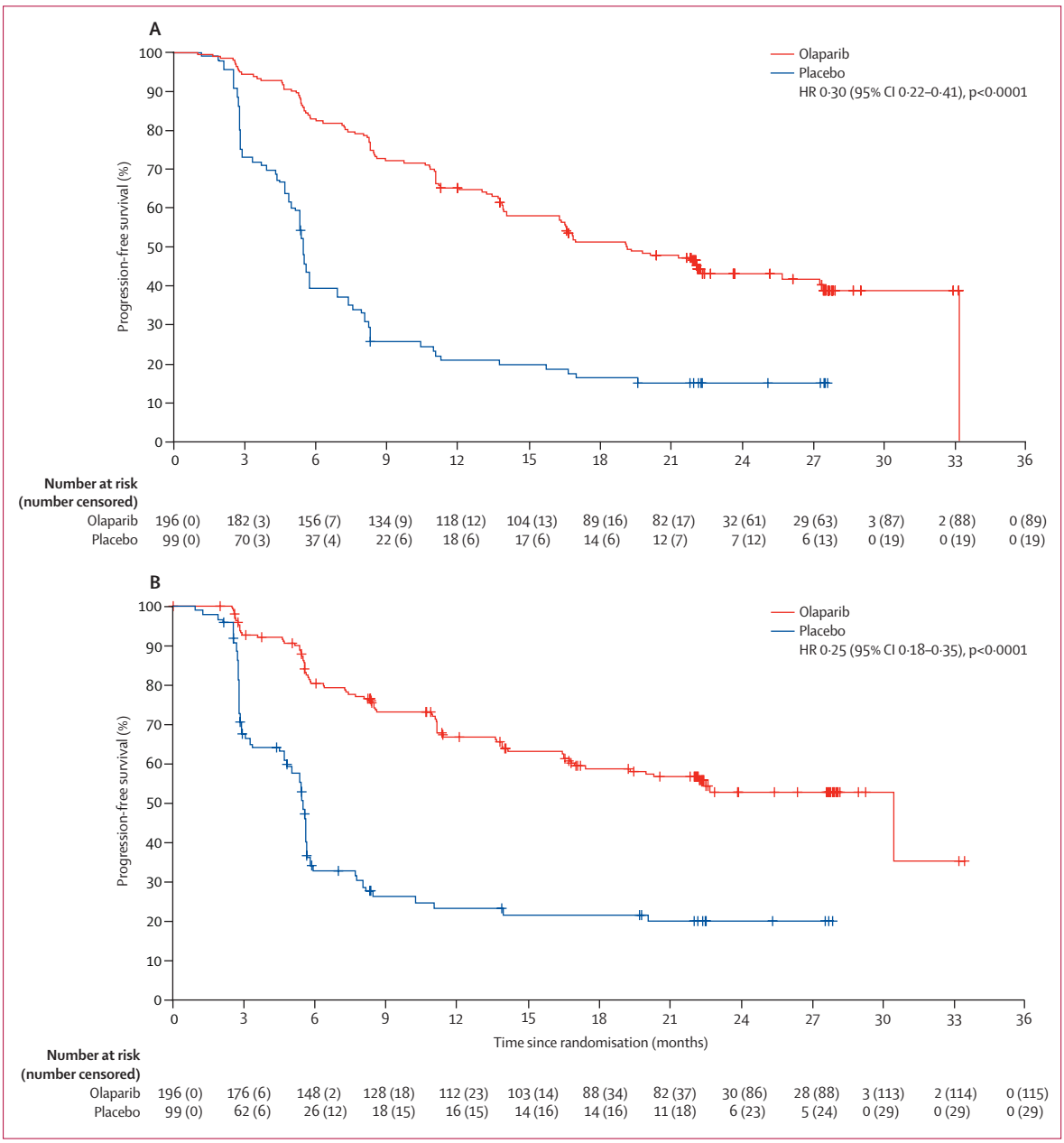

Figure 2: **Kaplan-Meier estimates of progression-free survival by (A) investigator assessment and (B) blinded independent central review**
HR=hazard ratio.

295 patients: 81 events in 196 patients in the olaparib group and 70 events in 99 patients in the placebo group; 51% maturity) also showed that median progression-free survival was significantly longer in patients receiving olaparib than in those given placebo (30·2 months [95% CI 19·8 to not calculable] *vs* 5·5 months [4·8–5·6]; figure 2B). A sensitivity analysis that adjusted conservatively for informative censoring was done to determine the potential effect of informative censoring on the results by blinded independent central review (appendix p 9).

A prespecified subgroup analysis of progression-free survival in 53 patients who had received bevacizumab therapy before their final platinum regimen prior to randomisation also showed that median progression-free survival was longer with olaparib than with placebo (17·0 months [95% CI 10·8 to not calculable] with olaparib *vs* 5·1 months [2·9–5·4] with placebo; HR [in favour of olaparib] 0·14, 95% CI 0·07–0·28; p<0·0001). We also completed a prespecified subgroup analysis of progression-free survival in the 286 (97%) patients who had a Myriad-confirmed deleterious, or suspected

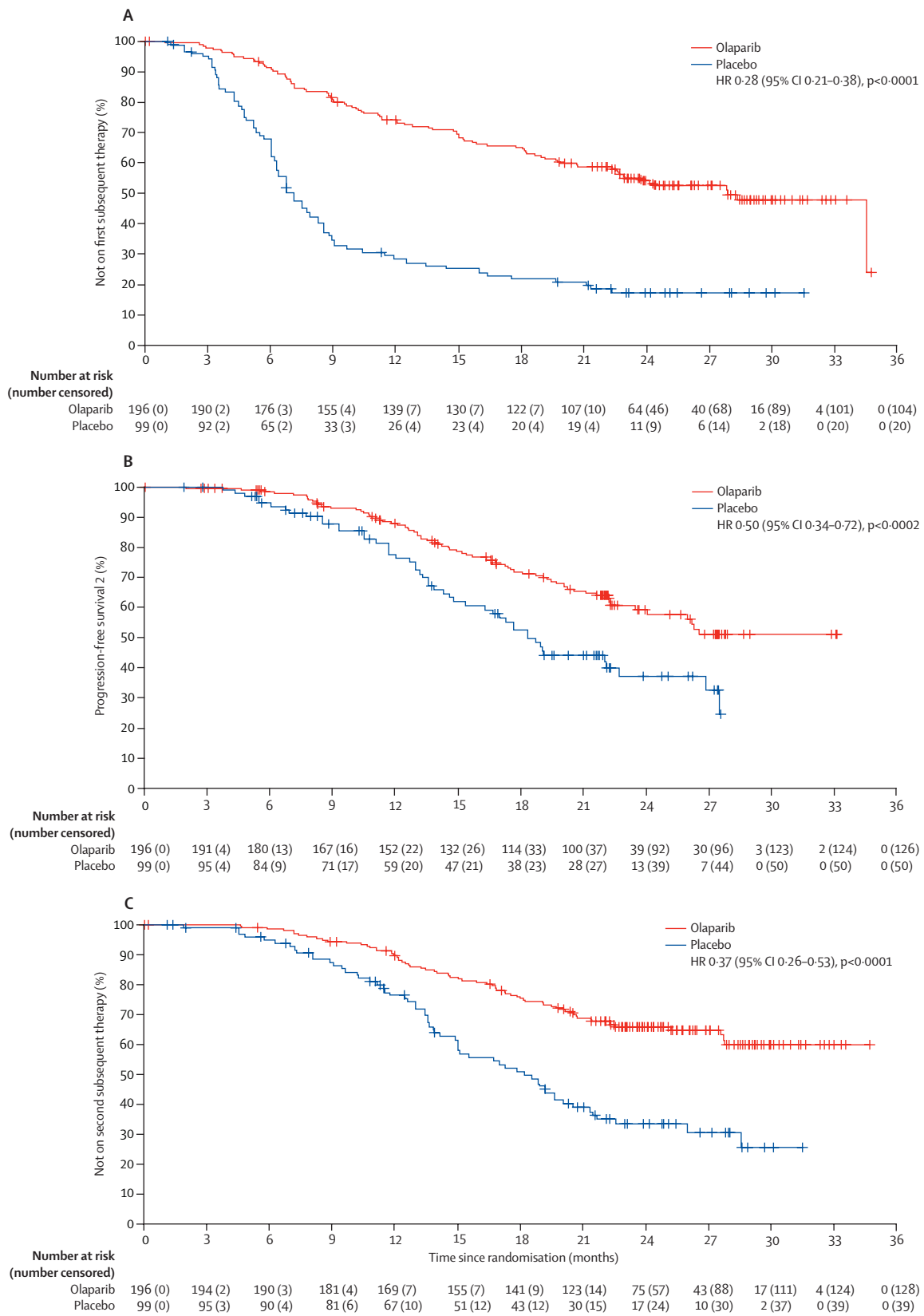

Figure 3: **Kaplan-Meier estimates of (A) time to first subsequent therapy or death; (B) time to second progression or death; and (C) time to second subsequent therapy or death**
HR=hazard ratio.

	Olaparib (n=195)			Placebo (n=99)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
Any adverse event	120 (62%)	63 (32%)	8 (4%)	76 (77%)	15 (15%)	3 (3%)
Non-haematological						
Nausea	143 (73%)	5 (3%)	0	33 (33%)	0	0
Fatigue or asthenia*	120 (62%)	8 (4%)	0	37 (37%)	2 (2%)	0
Vomiting	68 (35%)	5 (3%)	0	18 (18%)	1 (1%)	0
Diarrhoea	62 (32%)	2 (1%)	0	20 (20%)	0	0
Dysgeusia	52 (27%)	0	0	7 (7%)	0	0
Headache	48 (25%)	1 (1%)	0	13 (13%)	0	0
Abdominal pain	42 (22%)	5 (3%)	0	28 (28%)	3 (3%)	0
Decreased appetite	43 (22%)	0	0	11 (11%)	0	0
Constipation	40 (21%)	0	0	20 (20%)	3 (3%)	0
Cough	32 (16%)	1 (1%)	0	5 (5%)	0	0
Arthralgia	29 (15%)	0	0	15 (15%)	0	0
Pyrexia	26 (13%)	0	0	6 (6%)	0	0
Dizziness	25 (13%)	1 (1%)	0	5 (5%)	0	0
Dyspnoea	21 (11%)	2 (1%)	0	1 (1%)	0	0
Back pain	22 (11%)	0	0	11 (11%)	2 (2%)	0
Dyspepsia	22 (11%)	0	0	8 (8%)	0	0
Abdominal pain upper	21 (11%)	0	0	12 (12%)	0	0
Nasopharyngitis	21 (11%)	0	0	11 (11%)	0	0
Urinary tract infection	17 (9%)	1 (1%)	0	10 (10%)	0	0
Haematological						
Anaemia†	47 (24%)	36 (18%)	2 (1%)	6 (6%)	2 (2%)	0
Neutropenia‡	28 (14%)	8 (4%)	2 (1%)	2 (2%)	3 (3%)	1 (1%)
Thrombocytopenia§	25 (13%)	2 (1%)	0	2 (2%)	1 (1%)	0
Hypomagnesaemia	28 (14%)	0	0	10 (10%)	0	0
Blood creatinine increased	21 (11%)	0	0	1 (1%)	0	0
Leucopenia	17 (9%)	2 (1%)	1 (1%)	1 (1%)	0	0

Grade 1–2 adverse events, presented as haematological or non-haematological, occurring in at least 10% of patients in either treatment group are shown, together with all grade 3, 4, and 5 adverse events. The only grade 5 adverse event to occur was in the olaparib group. Data are n (%). Where indicated, the Medical Dictionary for Regulatory Activities (MedDRA)-preferred terms for some adverse events have been combined. *Includes patients with fatigue and patients with asthenia. †Includes patients with anaemia, haemoglobin decreased, haematocrit decreased, and red blood cell count decreased. ‡Includes patients with neutropenia, febrile neutropenia, neutropenic sepsis, neutrophil count decreased, granulocytopenia, and granulocyte count decreased. §Includes patients with thrombocytopenia, and platelet count decreased.

Table 2: **Adverse events**

deleterious, *BRCA1/2* mutation as part of this trial (190 patients in the olaparib group and 96 in the placebo group). Again, median progression-free survival was significantly longer in the olaparib group than in the placebo group (19·3 months [95% CI 16·5–27·3] with olaparib *vs* 5·5 months [5·0–5·8] with placebo; HR [in favour of olaparib] 0·33, 95% CI 0·24–0·44; p<0·0001).

The findings for several secondary endpoints also showed significantly improved outcomes with olaparib compared with placebo. Median time to first subsequent therapy (171 events in 295 patients: 92 [47%] in the olaparib group *vs* 79 [80%] in the placebo group; 58% maturity) was 27·9 months (95% CI 22·6 to not calculable) in the olaparib group versus 7·1 months (6·3–8·3) for placebo (figure 3A). Median time to second progression (119 events: 70 [36%] in the olaparib group *vs* 49 [50%] in the placebo group; 40% maturity) was not reached (95% CI 24·1 to not calculable) in the olaparib group versus 18·4 months (15·4–22·8) in the placebo group (figure 3B). Median time to second subsequent therapy (128 events: 68 [35%] *vs* 60 [61%]; 43% maturity) was not reached (95% CIs not calculable) compared with 18·2 months (15·0–20·5) in the placebo group (figure 3C). The immature overall survival data (72 events: 45 [23%] *vs* 27 [27%]; 24% maturity) showed no difference between the groups (HR 0·80 [95% CI 0·50–1·31], p=0·43; medians not reached in either group [95% CIs not calculable]). Results for time to earliest progression or death and time to study discontinuation or death are shown in the appendix (p 9).

Patient-reported outcomes showed no appreciable difference in quality of life for patients receiving olaparib compared with those receiving placebo. The primary analysis measure, mean change from baseline in TOI of the FACT-O (assessed in 185 [94%] of 196 patients in the olaparib group and 94 [95%] of 99 in the placebo group), was similar in both groups over the first 12 months (adjusted mean –2·90 points [95% CI –4·13 to –1·67] *vs* –2·87 points [–4·64 to –1·10]; estimated difference –0·03 points [–2·19 to 2·13]; p=0·98). Non-compliance with the FACT-O questionnaire resulted in the exclusion of 11 (6%) of 196 patients in the olaparib group and five (5%) of 99 patients in the placebo group from the analysis. Additional quality-of-life data will be published separately.

The most common adverse events of CTCAE grade 1–2 in both groups were nausea, fatigue or asthenia, vomiting, abdominal pain, and diarrhoea (table 2). However, the overall incidence of grade 3–5 adverse events was low in both groups. The most common adverse event of grade 3 or worse severity in the olaparib group was anaemia (table 2). 35 (18%) patients in the olaparib group had a blood transfusion compared with one (1%) in the placebo group. The incidence of neutropenia and thrombocytopenia of grade 3 or worse severity did not differ between the groups (table 2). Serious adverse events were experienced by 35 (18%) patients in the olaparib group and eight (8%) patients in the placebo group. The most common serious adverse events in the olaparib group were anaemia (seven [4%] patients), abdominal pain (three [2%] patients), and intestinal obstruction (three [2%] patients). The most common in the placebo group were constipation (two [2%] patients) and intestinal obstruction (two [2%] patients).

Overall, 72 (24%) patients died during the study—45 (23%) of 196 in the olaparib group and 27 (27%) of 99 in the placebo group. One (1%) patient in the olaparib group had a treatment-related adverse event (acute myeloid leukaemia) with an outcome of death (grade 5). No other deaths were considered to be related to study treatment by the investigator. The incidence in the safety population of acute myeloid leukaemia, myelodysplastic

syndrome, and chronic myelomonocytic leukaemia during the study and long-term follow-up was four (2%) patients in the olaparib group (two [1%] acute myeloid leukaemia, one [1%] myelodysplastic syndrome, and one [1%] chronic myelomonocytic leukaemia) and four (4%) patients in the placebo group (one [1%] acute myeloid leukaemia and three [3%] myelodysplastic syndrome). Overall, the incidence of all secondary malignancies during the study and long-term follow-up was six (3%) patients in the olaparib group and five (5%) patients in the placebo group (appendix p 10).

The frequency of adverse events leading to dose interruptions was higher in the olaparib group than in the placebo group (table 3). Similarly, dose reductions following adverse events were more common in the olaparib group than in the placebo group (table 3). A greater proportion of patients in the olaparib group discontinued study treatment because of toxicity than in the placebo group (table 3). Anaemia (six [3%] patients) and neutropenia (two [1%] patients) were the most common adverse events leading to discontinuation in the olaparib group. Adverse events that led to discontinuation in the placebo group were invasive ductal breast carcinoma (one [1%] patient) and thrombocytopenia (one [1%] patient). Full details of adverse events leading to dose modifications, interruptions, and discontinuations are shown in the appendix (pp 13–17).

	Olaparib (n=195)	Placebo (n=99)
Median relative dose intensity*	98·4% (84·7–99·9)	99·4% (98·1–100·0)
Median daily dose (mg)	597·6 (541·3–600·0)	598·4 (593·0–600·0)
Dose interruptions	88 (45%)	18 (18%)
Dose reductions	49 (25%)	3 (3%)
Discontinuations	21 (11%)	2 (2%)

Data are median (IQR) or n (%). *See appendix p 7 for further details on the relative dose intensity.

Table 3: **Dose modifications and discontinuations owing to adverse events**

Discussion

In this double-blind, randomised, phase 3 study, olaparib maintenance treatment (given as a tablet formulation) in patients with platinum-sensitive, relapsed ovarian cancer and a *BRCA1/2* mutation led to a significant improvement in progression-free survival compared with placebo, as evaluated both by the primary endpoint of investigator assessment and by blinded independent central review. In addition, analysis of the primary analysis measure for patient-reported outcomes, TOI of the FACT-O, did not show any appreciable detrimental effect on patients' quality of life for maintenance treatment with olaparib compared with placebo. The improvement in progression-free survival seen using the olaparib tablet formulation in this disease setting is compelling because patients were able to maintain a good quality of life while experiencing a delay in disease progression and, therefore, a delay until the symptoms associated with subsequent chemotherapy treatments.

The improvement in progression-free survival we recorded for patients with a *BRCA1/2* mutation is comparable to that reported with other PARP inhibitors in phase 2 and phase 3 trials in similar clinical settings; however, indirect comparisons cannot be considered definitive, particularly because of differences between the patient populations.[16–18] The subgroup analysis for progression-free survival in patients who had received treatment with bevacizumab prior to their final platinum regimen before randomisation in SOLO2 showed that bevacizumab did not alter the treatment effect for those receiving olaparib. The sensitivity analysis of progression-free survival by blinded independent central review, which was done to account for any potential bias from the investigator assessment, was consistent with the investigator-assessed primary endpoint. The HR in the sensitivity analysis was numerically slightly higher (0·25 *vs* 0·30). The increased median progression-free survival derived from the blinded independent central review analysis was possibly driven by informative censoring, whereby some patients who had progressed according to investigator assessment had not yet been shown to progress by blinded independent central review because scans were done every 12 weeks only, before submission for blinded independent central review assessment. Our sensitivity analysis that adjusted conservatively for informative censoring resulted in a median progression-free survival by blinded independent central review that was similar to the investigator assessment (appendix p 7). The primary progression-free survival analysis was done at a slightly lower maturity than that outlined in the statistical plan because, once we had determined the data cutoff for progression-free survival, the event rate slowed, leading to five fewer events than predicted.

Our study also showed a significant improvement in time to first subsequent therapy, time to second progression, and time to second subsequent therapy in favour of olaparib. The timing of first subsequent therapy typically marks a substantial treatment shift for patients with recurrent ovarian cancer, from an oral PARP inhibitor to intravenous chemotherapy, whereas the analysis of time to second subsequent therapy suggests that patients reach their second subsequent treatment without the potential occurrence of chemotherapy resistance countering the benefit they originally received on olaparib maintenance treatment. Of the secondary endpoints presented here, time to first and second subsequent therapy might therefore be especially clinically meaningful.[19,20] Furthermore, the analysis of time to second subsequent therapy included more events than did analysis of time to second progression or death (128 *vs* 119) because, at the time of data cutoff, some patients who had received a second subsequent therapy were not yet classed as having investigator-assessed disease progression following their first subsequent therapy. The overall data were immature at the time of this analysis.

Maintenance monotherapy with olaparib had previously been evaluated in Study 19, which showed a significant treatment benefit in both the overall study population (patients with platinum-sensitive, relapsed ovarian cancer) and the subpopulation of patients harbouring a *BRCA1/2* mutation.[2] Our SOLO2 data support the treatment benefit observed in Study 19 for patients with a *BRCA1/2* mutation, using a two-tablet twice-daily dosing schedule of olaparib. Patients with germline or somatic *BRCA1/2* mutations were eligible for the SOLO2 trial. An exploratory analysis comparing clinical outcomes for patients with somatic *BRCA1/2* mutations and germline *BRCA1/2* mutations in Study 19 showed a consistent efficacy benefit with olaparib treatment for both groups.[21] An analysis of the treatment benefit observed for patients with a somatic *BRCA1/2* mutation versus those with a germline *BRCA1/2* mutation in SOLO2 would therefore have provided an interesting opportunity for study; however, all patients who were enrolled and randomised in our trial harboured a germline *BRCA1/2* mutation. In line with other phase 3 PARP inhibitor data, the overall data in our study are immature and it is not yet known whether the progression-free survival improvement observed for patients receiving olaparib translates to a direct survival benefit. A preplanned analysis of overall survival at approximately 60% maturity (~177 overall survival events) will provide further information; these data will be reported in due course.

Nine (3%) patients in the overall study population, who were randomised on the basis of a locally identified *BRCA1/2* mutation, did not go on to have their *BRCA1/2* mutation confirmed as deleterious, or suspected deleterious, by the Myriad Genetics *BRCA* test as part of the trial. An analysis of progression-free survival that excluded these nine patients showed an HR in favour of olaparib that was highly consistent with the investigator-assessed primary endpoint. These data indicate that the progression-free survival improvement reported for patients receiving olaparib in our trial was not changed by the inclusion of patients who did not have Myriad confirmation of their *BRCA1/2* mutation.

Overall, the safety profile of the olaparib tablet was similar to that observed with the approved capsule formulation of olaparib.[12] The rate of anaemia of grade 3 or worse severity was higher in SOLO2 (olaparib: 38 [19%] of 195 patients; placebo: two [2%] of 99 patients [2%]) than in Study 19 (olaparib: seven [5%] of 136 patients; placebo: one [1%] of 128 patients).[12] These data could be explained by the observation that patients in SOLO2 had a longer exposure to olaparib than did patients in Study 19; the median duration of exposure in SOLO2 was 19·4 months (approximately 588·7 days) in the olaparib group versus 5·6 months (approximately 170·1 days) in the placebo group, whereas median exposure in Study 19 was 206·5 days in the olaparib group and 141·0 days in the placebo group.[12] The incidence of olaparib discontinuation due to adverse events showed that toxicity related to the 300 mg twice-daily maintenance olaparib tablet dose was manageable in most of these patients with dose modifications. Use of this approach in SOLO2 reduces the pill burden from 16 capsules to four tablets per day, providing a more convenient regimen for patients.[14] Several of the most common adverse events observed in patients receiving olaparib in SOLO2—namely, fatigue, nausea, anaemia, and vomiting—are considered to be class effects associated with PARP inhibitors.[16–18] The rates of neutropenia of grade 3 or worse were similar between the olaparib and placebo groups in SOLO2. Notably, some common adverse events of grade 3 or worse severity, such as thrombocytopenia, tachycardia, and liver enzyme elevation (alanine aminotransferase or aspartate aminotransferase increased), which have been reported by more than 10% of PARP inhibitor-treated patients in other trials,[16–18] were reported in no more than 1% of olaparib-treated patients in our trial. The rates of tachycardia, hypertension, anxiety, and insomnia were not increased in the olaparib group versus placebo. Taken together, these data highlight that olaparib does not show a significant interaction with liver or cardiovascular function, and does not have an appreciable direct negative effect on psychological function. Long-term follow-up data showed that the incidence of secondary malignancies, including acute myeloid leukaemia, myelodysplastic syndrome, and chronic myelomonocytic leukaemia, was also similar between both treatment groups in SOLO2.

To our knowledge, SOLO2/ENGOT Ov-21 provides the first phase 3 data for olaparib tablets as maintenance treatment in patients with platinum-sensitive, relapsed, serous ovarian cancer. Our results confirm that olaparib can achieve a significant prolongation of progression-free survival in this patient population with no appreciable detrimental effect observed for patients' quality of life. The favourable safety profile in SOLO2 enabled most patients receiving olaparib to maintain full dosing throughout their maintenance treatment.

Contributors

EP-L was responsible for the study design and for writing the manuscript. EP-L, JAL, FS, VG, RTP, AMO, JK, TH, AP, SP, MF, NC, PH, KF, IR-C, SB, JL, and PP were responsible for the accrual of patients, the conduct of the trial, and for obtaining the data. VG, ESL, and RB analysed the data. All authors interpreted the data, and reviewed the draft and final versions of the manuscript.

Study groups

Groupe des Investigateurs Nationaux pour l'Etude des Cancers Ovariens et du sein: EP-L, FS, IR-C, PP. Medical Research Council/National Cancer Research Institute: JAL, SB. SOLO2 US Consortium: RTP, JL. Princess Margaret Hospital Consortium: AMO. Israeli Society of Gynecologic Oncology: JK. Grupo Español de Investigación en Cáncer de Ovario: AP. Multicenter Italian Trials in Ovarian Cancer: SP. Australia New Zealand Gynaecological Oncology Group: MF. Mario Negri Gynecologic Oncology group: NC. Arbeitsgemeinschaft Gynaekologische Onkologie Austria: PH.

Declaration of interests

EP-L reports personal fees from AstraZeneca, Roche, and Pfizer, outside the submitted work. JAL reports grants and personal fees from AstraZeneca, outside the submitted work. FS reports personal fees from Roche and AstraZeneca, outside the submitted work. VG reports grants

from The University of Sydney during the conduct of this study. RTP reports personal fees from AstraZeneca during the conduct of the study. AP reports an advisory board role with AstraZeneca. SP reports personal fees from AstraZeneca during the conduct of the study, and grants from AstraZeneca, outside the submitted work. MF reports grants, personal fees, and advisory board membership from AstraZeneca, outside the submitted work. NC reports grants and personal fees from AstraZeneca, during the conduct of the study; and personal fees from Roche, PharmaMar, Clovis, Pfizer, and Tesaro, outside the submitted work. PH reports personal fees from AstraZeneca during the conduct of the study; and personal fees from Roche, Tesaro, Clovis, and PharmaMar, outside the submitted work. KF reports grants and personal fees from Daiichi Sankyo, during the conduct of the study; and grants from Kaken, Shionogi, Chugai, Immunogen, and Oncotherapy; grants and personal fees from AstraZeneca, Pfizer, Eisai, MSD, Taiho, Zeria, Ono, GlaxoSmithKline, and Lilly; and personal fees from Nihon Kayaku, Novartis, Kyowahakko Kirin, Janssen, and Asahikasei Medical, outside the submitted work. IR-C reports advisory board membership from AstraZeneca, outside the submitted work. SB reports personal fees and non-financial support from Tesaro, non-financial support from Clovis, and grants and non-financial support from AstraZeneca, outside the submitted work. JL reports study funding from AstraZeneca, during the conduct of the study; and honoraria and advisory board membership from AstraZeneca and advisory board membership from Tesaro and Genentech/Roche, outside the submitted work. ESL and RB report full-time employment from AstraZeneca during the conduct of this study. All remaining authors declare no competing interests.

Acknowledgments

We thank the patients for their participation in this study, and their families, plus all investigators and onsite personnel, and the contributing study groups. We thank Lizzie Wilkins (Mudskipper Business), who provided medical writing assistance funded by the sponsor. We thank Nathalie Le Fur (ARCAGY-GINECO) for her role in project management and John Salter (AstraZeneca) for his role in statistical analysis.

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